Paragraph beginning Page 2, Line 3:

The use of diluted carbon dioxide by inhalation for treating symptoms related to headaches, allergies, asthma, nervous disorders, and other common ailments was demonstrated in the 1940's and 1950's. The treatment protocols generally rely on breathing masks or other equipment for delivering relatively large volumes of dilute carbon dioxide for the patient to inhale through the mouth and/or the nose into the lungs until they become unconscious. The efficacy of this treatment depends upon the *systemic* effects of the inhaled gas and therefore require large volumes of gas. Typical carbon dioxide volumes inhaled were in the range from 0.5 to 25 liters of 30% to 70% carbon dioxide diluted in oxygen during a single treatment which was repeated several times a week for 25 to 50 treatments. While the use of inhaled carbon dioxide has proven to be quite effective for a number of indications, the wide spread use of carbon dioxide delivered in this manner never became popular. It is limited by the necessity of making the patient unconscious, the length of the treatment time and course, the necessarily large, bulky non-portable gas cylinders and the physician administration it requires. Most prior systems are so large and heavy they must be wheeled about using a dolly or a cart, and thus do not lend themselves to use outside of the hospital or home. While hand-held carbon dioxide dispensers have been proposed (for other purposes such as the treatment of hyperventilation), they are designed to deliver large volumes of dilute carbon dioxide for inhalation

G1

Paragraph beginning Page 3, Line 2

U.S. Patent No. 3,776,227, describes a hand-held dispenser that delivers dilute carbon dioxide intended for the treatment of hyperventilation by inhalation. In addition, this hand-held dispenser is not designed to deliver carbon dioxide at high concentrations which are chronically unbreathable. Other inhalation devices, systems, and methods for delivering carbon dioxide and other gases and aerosols to patients are described in U.S. Patent Nos. 3,513,843; 3,870,072; 3,974,830; 4,137,914; 4,554,916; 5,262,180; 5,485,827; and 5,570,683.

G2

Paragraph beginning Page 8, Line 15

In particular embodiments, the therapeutic gas may comprise essentially pure carbon dioxide or other pure therapeutic gas. By "essentially pure," it is meant that the carbon dioxide, or other therapeutic gas, is free from the significant presence of other gases, i.e., the total volume of gas will comprise at least 50% carbon dioxide, preferably at least 70% carbon dioxide, and more preferably 95% or greater. In addition to being free from other gases, the carbon dioxide will be free from other physiologically or biologically active components, such as drugs, surfactants, and other substances that, although present at relatively low concentrations, would have physiologic or biologic effect.

A3

Paragraph beginning Page 9, Line 33

A second aspect of the present invention comprises methods for generating a therapeutic dosage of carbon dioxide or other treatment gas. The methods comprise releasing from a hand-held dispenser a flow of therapeutic gas comprising from 1 cc/sec to 20 cc/sec of carbon dioxide. Preferably, the gas flow will consist essentially of carbon dioxide, i.e., be pure carbon dioxide as described above. Alternatively, however, the gas flow may comprise carbon dioxide present in a carrier gas, also as described above and/or with solid or liquid drugs or other substances. The hand-held dispenser will have an outlet suitable for delivering the gas to the patient. In a preferred embodiment, the outlet will be suitable for sealing in or against a human nostril. In an alternative embodiment, the outlet will be suitable for sealing in or against both human nostrils. In an alternative embodiment, the outlet will be suitable for sealing in or against a human mouth In yet another alternative embodiment, the outlet will be suitable for sealing around a human eye or both eyes. One or more treatment steps may be performed, with each step having a duration in the range from I second to 100 seconds, preferably from 2 seconds to 30 seconds, and often from 1 second to 20 seconds, depending on the condition being treated and on its severity. The total number of treatment steps will be selected depending on symptom severity. Typically mild symptoms require 1 or 2 treatment steps, moderate symptoms require 2 to 3 treatment steps, and severe symptoms require 3 to 8 treatment steps. The total number of treatment steps will be selected depending on the flow rate in order to provide a total target dosage of the carbon

A4

dioxide. Typically, the flow rates will be adjustable to a set point within the range from I cc/sec to 20 cc/sec. While such treatment flows and treatment times and number of treatment steps may initially be selected based on data, such as provided in Table I above, it will be appreciated that the patient will eventually learn the treatment regimen that leads to successful symptom relief for them personally.

a4

Paragraph beginning Page 10, Line 22

In yet another aspect, the present invention comprises dispensers for delivering therapeutic gases to a patient. The dispensers comprise a container holding a volume of the therapeutic gas, typically carbon dioxide or any of the other therapeutic gases described above. The dispenser further comprises a flow regulator that releases a flow of the therapeutic gas from the container to an outlet that is adapted to seal against a human nostril, mouth, or eye. Thus, the dispensers will be useful for delivering the therapeutic gas to the nostril, mouth, or eye for infusion of a mucous membrane according to the methods generally described above. As in the methods described above, the therapeutic gas is preferably carbon dioxide, either substantially pure carbon dioxide or carbon dioxide present in a carrier gas or liquid and/or combined with other active or non-active substances. The flow regulator preferably will be adjustable so that the patient can select a flow rate in the range from 1 cc/sec to 20 cc/sec, or within the other ranges set forth above. In an exemplary embodiment of the dispenser, the container comprises a cylinder that is capable of holding a volume of therapeutic gas, the adjustable flow regulator comprises a turnable cap at one end of the cylinder, and the outlet comprises a nozzle in the cap. The regulator may be turned to open the dispenser and initiate a flow of the carbon dioxide or other therapeutic gas. By then appropriately turning the cap, the flow rate can be adjusted to the user's preferred rate, and the outlet then inserted into or around the appropriate patient's orifice, in order to initiate infusion according to the methods described above.

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Paragraph beginning Page 12, Line 30

a6 1. Treatment of Allergic Rhinitis, Headache, and Other Common Ailments

It has been found by the inventors, that bathing the mucous membrane of the nose, nasal passages, and mouth, with gaseous carbon dioxide for times as short as one second can suppress the onset of acute irritation of the mucosa caused by triggers such as airborne and contact-transmitted allergens and/or antigens. Furthermore, chronic inflammation of the mucosa and associated distress, caused by extended exposure to allergens and/or antigens, may be relieved within a few minutes by repeating such carbon dioxide applications. A possible mechanism of action of the above described local carbon dioxide treatment is the following. Creating a high concentration of carbon dioxide *(hypercapnia)* by infusing it into the nasal passages causes a very fast lowering of the pH (making more acidic) of the mucous membranes depressing the neuronal activity (inhibiting inflammatory mediator release such as histamine) of the nerves that supply the nasal mucous membranes and connect directly to the brainstem. Asthma is known to be a comorbid disease to allergic rhinitis. Carbon dioxide is known to relax both central and peripheral airways in asthmatic adults. In addition, it is known that oxygenation is improved in patients with status asthmaticus, chronic obstructive pulmonary disease, and bronchiolitis by inhalation of helium/oxygen mixtures. Also, inhaled dilute nitric oxide improves the oxygenation and ventilation of most children with acute, hypoxic respiratory failure. For this reason, these respiratory ailments can be reduced or relieved by administering the above-described treatment using carbon dioxide or helium or nitric oxide. Furthermore, headaches (e.g., migraine headaches, tension-type headaches, cluster headaches, jaw pain, facial pain) are thought to be due to triggers creating a hyperexcitability state of nerves releasing inflammatory mediators such as histamine and serotonin. For this reason, headaches can be reduced or relieved by administering the above-described carbon dioxide treatment. Epilepsy, also a nervous hyperexcitability state, is known to be a comorbid disease to headaches and antiepileptic medications are used for migraine prevention. For this reason, epilepsy can be reduced or relieved by administering the above-described carbon dioxide treatment. A convenient hand-held easily controlled dispenser of carbon dioxide has been found to be an adequate and optimum means for practicing this carbon dioxide application process. Furthermore, other gases such as nitric oxide, oxygen, helium, and others may be administered similarly as therapeutic gases via the convenient hand-held easily controlled dispenser.

Paragraph beginning Page 13, Line 29

Essential elements of successful suppression of symptoms, pain, and inflammation through use of carbon dioxide are the convenient dispensing of the carbon dioxide or other therapeutic gas at a time, at a controlled flow rate, and for a duration selected by the user. Because of the ability of carbon dioxide to quickly or immediately suppress an acute attack, the means for carbon dioxide application should be available immediately, upon demand by the user, at the time when symptoms appear upon exposure to a trigger. If circumstances do not permit such immediate application, the means for application must be available continuously to relieve the consequent inflammation and distress as soon as possible after the exposure when circumstances permit its use.

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Paragraph beginning Page 14, Line 5

Furthermore, it is desirable that the user be able to conveniently but precisely and controllably select a rate and duration of carbon dioxide flow that lies between the lower limit of effectiveness and the upper limit of tolerance. It has been found that these limits are subjective, depending upon the personal sensitivities of the individual user, the degree and extent of the user's symptoms, and the site of carbon dioxide infusion. Flows as low as 1 cc/sec for 1-2 seconds into the nose are effective for suppression of onset of acute allergic symptoms, whereas flows of 4-5 cc/sec for 5-10 seconds are typically selected for optimum relief from a mild chronic allergy attack. For severely inflamed mucosa and/or for injection into the mouth, flows as high as 10 cc/sec or higher for as long as 15 seconds or longer often are selected for optimum relief. For the treatment of tension and migraine headaches, the flow durations can be substantially longer, as generally set forth in the Dosage Guideline (Table 1) above.

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Paragraph beginning Page 15, Line 9

Most often the major site of general distress is the head, for which the preferred mode of carbon dioxide infusion is directly into a nostril. While not inhaling the carbon dioxide, carbon dioxide is infused into a nostril and continued until full relief is obtained. This usually occurs after the carbon dioxide flow is detected exiting the opposite nostril and/or the mouth. With an allergy attack, often the nasal passages are blocked by swelling of the mucosa, in which case sufficient pressure automatically builds to open and infuse the passage through each nostril separately. When both passages are clear, each can be infused separately by holding one nostril closed while opening the mouth, or both can be perfused by closing the mouth and allowing the flow into one nostril to exit through the other. Frequently inflammation, swelling, and itching of the upper mouth accompany the irritant reaction to the allergen and/or antigen. In this case, it is most effective to infuse the carbon dioxide through pursed lips directly into the mouth with exit through the nose while the breath is held. Specific techniques may be learned by experience and optimum procedures will depend on personal preference. The ability of the patient to optimize the treatment protocol is enabled by the fully adjustable flow rate and selectable infusion site afforded by the devices of the present invention.

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Paragraph beginning Page 19, Line 4

Referring now to Fig. 9A, an alternative dispenser head embodiment 80 will be described. The dispenser head 80 is similar to the embodiment described above with respect to Figs. 1-5, except that the needle perforation and flow regulating aspects of the assembly are separated. In particular, the dispenser head 80 comprises a lower collar 82 and a flow-regulating cap 84 threadably mounted to an upper end of the lower collar. Needle 86 is secured in the lower portion of the flow-regulating cap 84 and includes two tapered regions. The first tapered region 88 acts as the needle tip which penetrates seal 90 which is mounted over the upper end 92 of a high pressure gas cylinder 94. The seal 90 extends above threaded neck 96 of the gas cylinder 94. The lower collar 82 is threadably mounted over the threaded neck 96 in such a way that the seal 90 extends into a high pressure gas chamber 98 within the upper end of the lower collar 82. An O-ring seal 100 is provided to inhibit leakage of the high pressure gas.

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Paragraph beginning Page 21, Line 8

The preferred dispenser embodiment shown in Fig. 9B retains the major features of the initial embodiment described previously but, in addition, it can be seen that the single dispenser head part of the initial embodiment has been replaced by a two-part assembly consisting of a head 16' and a collar 94'. The head 16' is similar to the initial dispenser head 16 in that it incorporates a perforating and flow-regulating needle 18' along with ports 20' for delivering the dispensed gas. The collar 94' is screwed onto the carbon dioxide cartridge neck 15' and fixed there against rotation, e.g. by a jam thread 14'. The head 16' is screwed onto a fine thread 96' on the collar. The fine thread 96' (e.g., 48-56 threads/inch) permits a much finer rotational adjustment than the coarse thread 14' (typically 28 threads/inch) on the cartridge neck.

A11

Paragraph beginning Page 21, Line 18

The preferred needle configuration, shown in Fig. 4B, permits obtaining the required very small change in orifice area by a relatively large axial displacement of the needle. The lower most portion of the needle, over a distance approximately equal to the thickness of the cartridge sealing cap 30, has essentially the same shape and size as the puncture point 97 shown in Fig. 4A as employed in the initial embodiment of the dispenser. The configuration of this point is an optimum compromise between the strength of a blunt point and the reduced force requirement of a sharp point in the puncture process. However, the needle region 98' beyond the puncture point, that is adjacent to the perforated cap wall, determines the size of the annular flow-controlling orifice of the valve seat 42 when the needle is partially withdrawn. The configuration of the flow-controlling seat region 98' of the needle is advantageous for obtaining the required flow regulation characteristics of the dispenser. Above the needle region 98' the needle may be of still larger diameter. For example, in one embodiment the needle diameter was approximately 1 mm or .04 inches.

Paragraph beginning Page 22, Line 16

A12

5. Embodiment with Separate Puncture and Valve Seat Means

Referring now to Fig. 9A, an alternative dispenser head embodiment 80 will be described. The dispenser head 80 is similar to the embodiment described above with respect to Figs. 1-5, except that the needle perforation and flow regulating aspects of the assembly are separated. In particular, the dispenser head 80 comprises a lower collar 82 and a flow-regulating cap 84 threadably mounted to an upper end of the lower collar. Needle 86 is secured in the lower portion of the flow-regulating cap 84 and includes two tapered regions. The first tapered region 88 acts as the needle tip which penetrates seal 90 which is mounted over the upper end 92 of a high pressure gas cylinder 94. The seal 90 extends above a threaded neck 96 of the gas cylinder 94. The lower collar 82 is threadably mounted over the threaded neck 96 in such a way that the seal 90 extends into a high pressure gas chamber 98 within the upper end of the lower collar 82. An O-ring seal 100 is provided to inhibit leakage of the high pressure gas.

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Paragraph beginning Page 25, Line 26

As shown in Fig. 14, kits according to the present invention will include a carbon dioxide or other therapeutic gas dispenser 10 in combination with instructions for use 12. The instructions for use will include written instructions corresponding to any of the methods of the present invention as described above. In particular, the written instructions will refer specifically to use of the dispenser 10 in a way to relieve symptoms of common ailments as described above. In addition to the dispenser 10 and written instructions 12, the kits will usually include packaging, for example in the form of a cylindrical container 114 having a removable cap 116. The dispenser 10 and instructions for use 112 will conveniently be packaged together within the container and covered by the cap 116.

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Paragraph beginning Page 26, Line 18

Fig. 15 shows experimental measurements of the flow rate characteristics for the one-piece and two-piece embodiments with the initial needle configuration, as well as those for the combination of preferred two-piece dispenser head with the preferred needle configuration. Data obtained using the initial needle configuration was too erratic to be plotted, i.e., having large hysteresis and other non-reproducible flow characteristics. The dashed lines show the general sensitivity of flow rate to head rotation for those models, however. It can be seen that the

A14

preferred needle configuration 18' gives the greatly improved reproducible control and sensitivity required for self-treatment by the patient.

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Paragraph beginning Page 26, Line 31

The models of the initial one-piece embodiment (test device) were used in these preliminary human application tests. The test device was a hand-held, multi-dose, disposable, dispenser that was approximately 3 to 4 inches long and 6/8 to 7/8 inches in diameter. The device consisted of a plastic twist-top flow regulator mounted on top of a pressurized steel cartridge containing liquid carbon dioxide. The tip of the flow regulator has a nosepiece that is the optimal size and configuration to place against and seal off a nostril for administration of the gas. In a number of subjects, the effective nasal and oral carbon dioxide flow rates, and maximum tolerable nasal and oral flow rates, were measured using a laboratory apparatus. This apparatus consisted of a flow regulator connected via tubing to a flow meter and a large tank of carbon dioxide. These flow data were used, together with the number of seconds gas was administered during therapy, to calculate the estimated dose of gas in milliliters.

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Paragraph beginning Page 31, Line 14

Using the more stringent HIS efficacy outcome measures (that exclude mild headaches, with relief defined as moderate or severe reduced to mild to none) the treatment had the same average *headache free efficacy* of 80% (migraine=75%, tension=80%) for headache at 30 minutes as in the above analysis (see Table VI below). With these criteria, the treatment had an 84% *headache relief efficacy* (migraine=100%, tension=77%) for headache at 30 minutes. Considerable headache relief also was obtained at 15 minutes post-treatment (*headache relief efficacy*=72%; *headache free efficacy*=72%).

Q16

In the Drawings:

Please amend Fig.7 as indicated in red on a copy of the drawing as filed with the original, uncorrected amendment, which also included a clean copy of the drawing. This amendment corrects an obvious error, as the cross-section line 8-8 in Figure 7 does not match the cross-